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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 275/28, 335/16, 233/07, 271/26, C07D 295/16, 203/04, 205/02, A61K 31/17, 31/16, 31/33

A1

(11) International Publication Number: **WO 99/07672**

(43) International Publication Date: 18 February 1999 (18.02.99)

(21) International Application Number: PCT/DK98/00337

(22) International Filing Date: 24 July 1998 (24.07.98)

(30) Priority Data:

0906/97	5 August 1997 (05.08.97)	DK
60/055,193	11 August 1997 (11.08.97)	US

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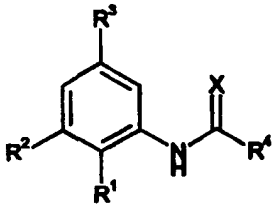
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: DERIVATIVES OF 2,5- AND 3,5-DISUBSTITUTED ANILINES, THEIR PREPARATION AND USE

(57) Abstract

Substituted anilines of general formula (I) wherein R^1, R^2, R^3, R^4 and X are defined in the description, compositions thereof and methods for preparing the compounds are described. The compounds are useful for the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the urogenital system, the gastrointestinal system and the endocrinological system.



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Derivatives of 2,5- and 3,5-disubstituted anilines, their Preparation and Use

FIELD OF THE INVENTION

The present invention relates to derivatives of 2,5- and 3,5-disubstituted anilines, to methods for their preparation, to compositions comprising these compounds, to the use of these compounds as medicaments and their use in therapy e.g. in the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the urogenital system, the gastrointestinal system and the endocrinological system.

BACKGROUND OF THE INVENTION

Potassium channels play an important role in the physiological and pharmacological control of cellular membrane potential. Amongst the different types of potassium channels are the ATP-sensitive (K_{ATP}-) channels which are regulated by changes in the intracellular concentration of adenosine triphosphate. The K_{ATP}-channels have been found in cells from various tissues such as cardiac cells, pancreatic cells, skeletal muscles, smooth muscles, central neurones and adenohypophysis cells. The channels have been associated with diverse cellular functions, as for example hormone secretion (insulin from pancreatic beta-cells, growth hormone and prolactin from adenohypophysis cells), vasodilation (in smooth muscle cells), cardiac action potential duration and neurotransmitter release in the central nervous system.

Modulators of the K_{ATP}-channels have been found to be of importance for the treatment of various diseases. Certain sulfonylureas which have been used for the treatment of non-insulin-dependent diabetes mellitus act by stimulating insulin release through an inhibition of the K_{ATP} -channels on pancreatic beta-cells.

The potassium channel openers, which comprise a heterogeneous group of compounds, have been found to be able to relax vascular smooth muscles and have therefore been used for the treatment of hypertension.

In addition, potassium channel openers can be used as bronchodilators in the treatment of asthma and various other diseases.

Furthermore, potassium channel openers have been shown to promote hair growth, and have been used for the treatment of baldness.

Potassium channel openers are also able to relax urinary bladder smooth muscle and can therefore be used for the treatment of urinary incontinence. Potassium channel openers which relax smooth muscle of the uterus can be used for treatment of premature labour.

Since some K_{ATP}-openers are able to antagonize vasospasms in basilar or cerebral arteries the compounds of the present invention can be used for the treatment of vasospastic disorders such as subarachnoid haemorrhage and migraine.

Potassium channel openers hyperpolarize neurons and inhibit neurotransmitter release, and therefore the present compounds may be useful for the treatment of various diseases of the central nervous system, e.g. epilepsia, ischemia and neurodegenerative diseases, and for the treatment of pain.

Recently it has been shown that diazoxide (7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide) and certain 3-(alkylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide derivatives inhibit insulin release by an activation of K_{ATP}-channels on pancreatic beta-cells (Pirotte B. et al., *Biochem. Pharmacol.* **1994**, *47*, 1381-1386; Pirotte B. et al., *J. Med. Chem.* **1993**, *36*, 3211-3213. Diazoxide has furthermore been shown to delay the onset of diabetes in BB-rats (Vlahos W.D. et al., *Metabolism* **1991**, *40*, 39-46. In obese Zucker rats diazoxide has been shown to decrease insulin secretion and increase insulin receptor binding and consequently improve glucose tolerance and decrease weight gain (Alemzadeh R. et al., *Endocrinol.* **1993**, *133*, 705-712). It is expected that such potassium channel openers can be used for treatment of diseases characterized by an overproduction of insulin and for the treatment and prevention of diabetes.

Derivatives of 3,5-bis(trifluoromethyl)aniline, 3,5-dichloroaniline, 2,5-bis(trifluoromethyl)aniline and other, similarly substituted anilines have been previously

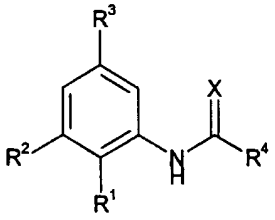
claimed as crop protecting agents, antibacterials, anti-snails and for other uses, but not as potassium channel openers:

FR 1507886, Chem. Abstr., 70, 19821k, 1969; Agfa A.G., DE 1116534, 1961, Chem. Abstr., EN, 56, 10329h, 1962; Ciba-Geigy AG, Basel (Schweiz), DE 2617163, 1976, Chem. Abstr., EN, 86, 55279; Hoechst, DE 2546271, 1977, Chem. Abstr., EN, 87, 64057; Dow Chemical Co., US 3755505, 1970, Chem. Abstr., EN, 79, 104972; Ciba, NL 6516437, 1966, Chem. Abstr., EN, 66, 2329j, 1967; CIBA Ltd., FR 1511325, 1966, Chem. Abstr., EN, 71, 91052y, 1969; CIBA, CH 495703, 1970, Chem. Abstr., EN, 74, 79613; Ciba, US 3592932, 1971; CIBA Ltd., DE 1803084, 1967, Chem. Abstr., EN, 71, 91119a, 1969; Bayer AG, DE 2623847, 1977, Chem. Abstr., EN, 88, 120822; Labor.J.Berthier S.A., ZA 6706114, 1968, Chem. Abstr., EN, 70, 57467g, 1969.

Amides from 3,5-dichloroaniline and linear aliphatic carboxylic acids have been described as antibacterials (*J. Med. Chem.* **1983**, *26*, 1741).

DESCRIPTION OF THE INVENTION

The present invention relates to derivatives of 2,5- and 3,5-bis-substituted anilines of the general formula I:



I

wherein

R^1 is hydrogen, trifluoromethyl or halogen;

R^2 is hydrogen, trifluoromethyl or halogen;

R^3 is trifluoromethyl or halogen;

R^4 is straight or branched alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl, optionally substituted with C_{3-8}-cycloalkyl or aryloxy; or

aryl optionally substituted with halogen, cyano or trifluoromethyl; or

heterocyclyl optionally substituted with halogen, cyano or trifluoromethyl; or

aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or

Y-R^5, wherein Y is -O- or -N(R^6)-

wherein R^5 is straight or branched alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl, optionally substituted with C_{3-8}-cycloalkyl, imidazolyl, methoxyphenyl or 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl; or

aryl optionally substituted with halogen, cyano or trifluoromethyl;

heterocyclyl, optionally substituted with halogen, cyano, benzyl or trifluoromethyl; or

aryloxy, optionally substituted with halogen, cyano or trifluoromethyl;

R^6 is hydrogen; or

straight or branched alkyl optionally substituted with C_{3-8}-cycloalkyl; or

aryl optionally substituted with halogen, cyano or trifluoromethyl; or

heterocyclyl, optionally substituted with halogen, cyano or trifluoromethyl; or

aryloxy optionally substituted with halogen, cyano or trifluoromethyl;; or

R^5 and R^6 are linked to form a 3-8 membered ring which is optionally substituted with straight or branched alkyl or pyrrolidinylcarbonylmethyl; or

aryl optionally substituted with halogen, cyano or trifluoromethyl; or

furoyl, benzoyl, acetyl, hydroxy, aminocarbonyl; or

piperidinyl; or

R^5 and R^6 are linked to form a saturated or unsaturated isoquinolin ring, optionally substituted with methoxy or dimethoxybenzyl;

X is O or S;

or a pharmaceutically acceptable salts thereof.

with the proviso that R^1 and R^2 are not both hydrogen at the same time;

and further provided that when R^2 is hydrogen and R^1 and R^3 are chloro, then

R^4 can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;

R^4 can not be methyl, unsubstituted or monosubstituted with aryl, aryloxy, alkylamino, arylamino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium or aminoalkyl;

R^4 can not be n-alkyl;

R^4 can not be $-(CH_2)_3-OAr$;

R^4 can not be 2,6-dimethylpiperidin-1-yl, methylamino, butylamino, benzylamino, arylamino, dimethylamino, diethylamino, dipropylamino, dibenzylamino, (methyl)(propargyl)amino, (1-phenylcyclohex-1-yl)methylamino, 4-heteroarylpiperazin-1-yl, (6-methylpyridin-2-yl)methylamino, (4-pyridinylmethyl)(methyl)amino or 2,5-dimethylpyrrolidin-1-yl.

When R^2 is hydrogen and R^1 and R^3 are trifluoromethyl, then

R^4 can not be methyl, pyridyl, ethyl, n-propyl or 2-propylbutyl.

When R^1 is hydrogen and R^2 and R^3 are chloro, then

R^4 can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;

R^4 can not be methyl, unsubstituted or monosubstituted with aryl, aryloxy, alkylamino, arylamino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium or aminoalkyl;

R^4 can not be n-alkyl, cyclopropyl or 2-propylbutyl;

R^4 can not be $-(CH_2)_3-OAr$ or $-CH(OH)CH_3$;

R^4 can not be arylamino, methylamino, isobutylamino, butylamino, 3-hydroxypropylamino, dimethylamino, [1-methyl-1-(4-bromophenyl)ethyl]amino, (methyl)(propargyl)amino, (isopropyl)(propargyl)amino, di(n-butyl)amino, dibenzylamino or (benzyl)(n-butyl)amino.

When X is oxygen, R^1 is hydrogen and R^2 and R^3 are trifluoromethyl, then

R^4 can not be heterocyclyl;

R^4 can not be methyl, unsubstituted or monosubstituted with heteroaryloxy, ammonium, acyl, 1-oximoalkyl, heterocyclyl or 1-iminoalkyl;

R^4 can not be 2-propylbutyl or cyclopropyl;

R^4 can not be benzylamino, 2-phenylethylamino, (1-phenyl)ethylamino, 4-chlorobenzylamino, 2-chlorobenzylamino, 2-(4-chlorophenyl)ethylamino, 3,4-dichlorobenzylamino, (3,4-dichlorobenzyl)(methyl)amino, (2-ethylhex-1-yl)amino, isopropylamino, propylamino, butylamino or 4-methyl-1-piperazinyl.

When X is sulfur, R^1 is hydrogen and R^2 and R^3 are trifluoromethyl, then
R^4 can not be benzylamino, 3,4-dimethylbenzylamino, 4-methoxybenzylamino, 3,4-dichlorobenzylamino, (2-hydroxy-1-methyl-2-phenylethyl)(methyl)amino, isopropylamino, n-propylamino, n-pentylamino, 4-chlorobenzylamino, 1-piperidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, 2,6-dimethyl-4-thiomorpholinyl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl or 4-ethoxycarbonylpiperazin-1-yl;

When R^1 is chloro, R^2 is hydrogen and R^3 is trifluoromethyl, then
R^4 can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
R^4 can not be methyl, unsubstituted or substituted with aryl, heteroaryl, aryloxy, amino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium, aminoalkyl;
R^4 can not be unsubstituted n-alkyl, cyclopropyl, isopropyl, isobutyl, benzyl, 2-ethylpropyl, 2-propylbutyl;
R^4 can not be diisopropylamino, 2,6-dimethylpiperidin-1-yl, methylamino, dimethylamino, (1,1-dimethylpropargyl)amino, ethylamino, butylamino, (2-hydroxyprop-1-yl)amino or 1-adamantylamino.

Within its scope the invention includes all diastereomers and enantiomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixtures thereof.

The scope of the invention also includes all tautomeric forms of the compounds of formula I.

The salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethanesulfonic, picric and the like, and include acids related to the pharmaceutically acceptable salts listed in *J. Pharm. Sci.* **1977**, *66*, 2, and incorporated herein by reference, or lithium, sodium, potassium, magnesium and the like.

The term "heterocyclyl" as used herein refers to: a monocyclic unsaturated or saturated system containing one, two or three hetero atoms selected from nitrogen, oxygen and sulfur and having 5 members, e.g. a radical derived from pyrrole, furan, thiophene, pyrroline, dihydrofuran, dihydrothiophene, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, thiazole, isoxazole, isothiazole, 1,2,3-oxadiazole, furazan, 1,2,3-triazole, 1,2,3-thiadiazole or 2,1,3-thiadiazole; an aromatic monocyclic system containing two or more nitrogen atoms and having 6 members, e.g. a radical derived from pyrazine, pyrimidine, pyridazine, 1,2,4-triazine, 1,2,3-triazine or tetrazine; a non-aromatic monocyclic system containing one or more hetero atoms selected from nitrogen, oxygen and sulfur and having 6 or 7 members, e.g. a radical derived from pyran, thiopyran, piperidine, dioxane, oxazine, isoxazine, dithiane, oxathine, thiazine, piperazine, thiadiazine, dithiazine, oxadiazine or oxoazepane as well as the corresponding benzo and dibenzo derivatives.

Alkyl refers to lower straight, cyclic, bicyclic, fused or branched alkyl having 1 to 15 carbon atoms, preferentially 1 to 6 carbon atoms. Aryl refers to phenyl or phenyl substituted with alkyl or phenyl, or phenyl fused with cycloalkyl, or polycyclic aromatic systems such as naphthyl, anthracenyl, phenanthrenyl, fluorenyl, etc. Alkylene refers to lower straight, cyclic, fused or branched alkylene having 1 to 15 carbon atoms, preferentially 1 to 6 carbon atoms. Heteroaryl refers to any of the possible isomeric, unsubstituted or alkyl-substituted pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, as well as the corresponding benzo and dibenzo derivatives or other fused ring-systems thereof. Heteroaryl is also intended to mean the partially or fully hydrogenated derivatives of the heterocyclic systems enumerated above. Alkoxy refers to -O-alkyl and aryloxy refers to -O-aryl. Cyano refers to -CN, hydroxy refers to -OH, amino refers to $-NH_2$ and nitro refers to $-NO_2$. Dialkylamino refers to $-N(alkyl)_2$. Alkylarylamino refers to -N(alkyl)(aryl) and diarylamino refers to $-N(aryl)_2$. Halogen refers to -F, -Cl, -Br and -I. Aralkyl refers to -alkylene-aryl. Alkylthio refers to -S-alkyl and arylthio refers to -S-aryl. Alkoxycarbonyl refers to -CO-O-alkyl and aminocarbonyl refers to $-CO-NH_2$, -CONH(alkyl), -CONH(aryl), $-CO-N(alkyl)_2$, -CO-N(alkyl)(aryl) or $-CO-N(aryl)_2$. Acylamino refers to -NH-CO-(alkyl), -NH-CO-(aryl), -N(alkyl)-CO-alkyl or -N(alkyl)-CO-aryl. A leaving group refers to a group or atom capable of existing in solution as a negatively charged species, or a positively charged group or atom.

The term "C_{2-6}-alkenyl" as used herein refers to an unsaturated hydrocarbon chain having 2-6 carbon atoms and one double bond such as e.g. vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl.

The term "C_{2-6}-alkynyl" as used herein refers to unsaturated hydrocarbons which contain triple bonds, such as e.g. $-C\equiv CH$, $-C\equiv CCH_3$, $-CH_2C\equiv CH$, $-CH_2CH_2C\equiv CH$, $-CH(CH_3)C\equiv CH$, and the like.

The compounds of the present invention interact with the potassium channels and hence act as openers or blockers of the ATP-regulated potassium channels, making them potentially useful for the treatment of various diseases of the cardiovascular system, e.g. cerebral ischemia, hypertension, ischemic heart diseases, angina pectoris and coronary heart diseases; the pulmonary system; the urogenital system; the gastrointestinal system; the central nervous system and the endocrinological system.

The compounds of the present invention may also be used for the treatment of diseases associated with decreased skeletal muscle blood flow such as Reynauds disease and intermittent claudication.

Further, the compounds of the invention may be used for the treatment of chronic airway diseases, including asthma, and for treatment of detrusor muscle instability secondary to bladder outflow obstruction and therefore for kidney stones by aiding their passage along the ureter. Potassium channel openers also relax urinary bladder smooth muscle, thus, the compounds of the present invention can be used for the treatment of urinary incontinence.

The present compounds could also be used for treatment of conditions associated with disturbances in gastrointestinal mobility such as irritable bowel syndrome. Additionally these compounds can be used for the treatment of premature labor and dysmenorrhea.

Further, potassium channel openers promote hairgrowth, therefore, the compounds of the present invention can be used for the treatment of baldness.

In diseases such as nesidioblastosis and insulinoma in which a hypersecretion of insulin causes severe hypoglycemia the compounds of the present invention may be used to reduce insulin secretion. In obesity hyperinsulinemia and insulin resistance is very frequently encountered. This condition could lead to the development of non insulin dependent diabetes (NIDDM). Potassium channel openers and hence the compounds of the present invention may be used for counteracting the hyperinsulinemia and thereby prevent diabetes and reduce obesity. In overt NIDDM treatment of hyperinsulinemia with potassium channel openers, and hence the present compounds, can be of benefit in restoring glucose sensitivity and normal insulin secretions.

In early cases of insulin dependent diabetes (IDDM) or in prediabetic cases, potassium channel openers and hence the present compounds may be used to induce beta-cell rest which may prevent the progression of the autoimmune disease. The title compounds may be used to reduce beta-cell degeneration in type 1 or type 2 diabetes and to normalize insulin secretion and improve insulin resistance in type 2 diabetes.

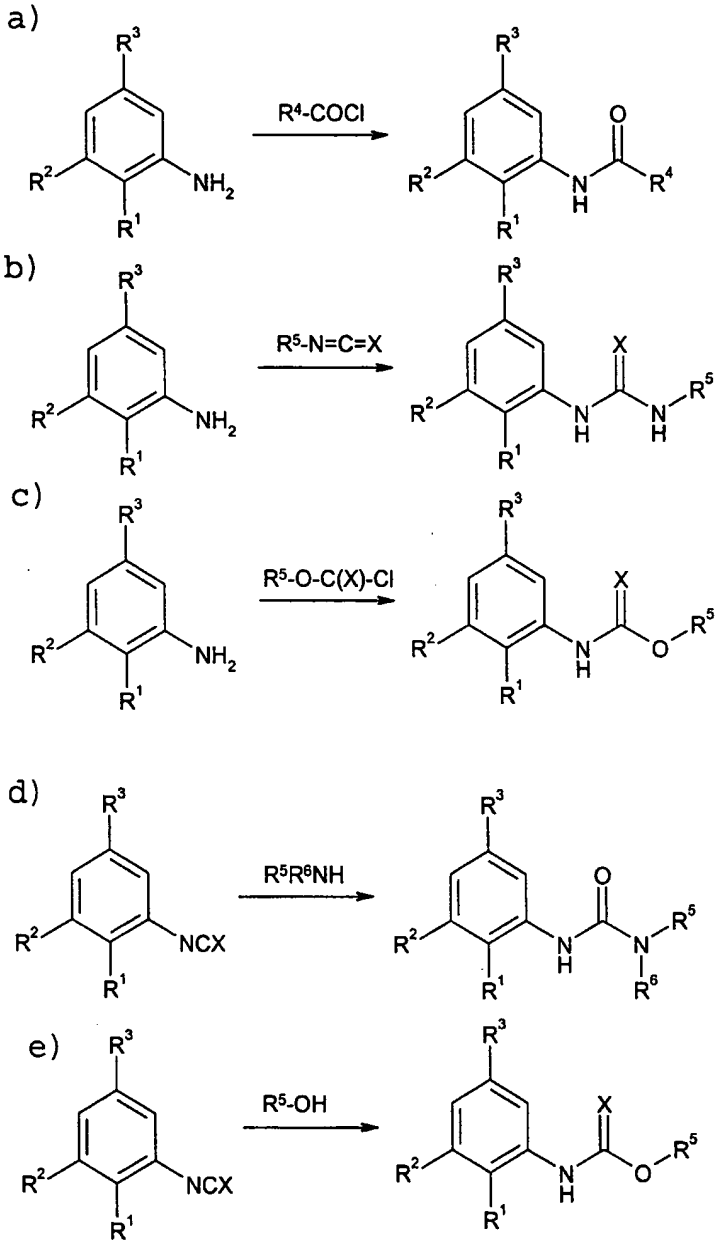
Compounds of the present invention which act as blockers of K_{ATP}-channels may be used for the treatment of NIDDM.

Preferably, the compounds of the present invention may be used for treatment or prevention of diseases of the endocrinological system such as hyperinsulinaemia and diabetes.

Accordingly, in another aspect the invention relates to a compound of the general formula I or a pharmaceutically acceptable salt thereof for use as a therapeutically acceptable substance, preferably for use as a therapeutically acceptable substance in the treatment of hyperinsulinaemia and treatment or prevention of diabetes.

Furthermore, the invention also relates to the use of the inventive compounds of formula I as medicaments useful for treating hyperinsulinaemia and treating or preventing diabetes .

The compounds of this invention can be prepared by many different routes, obvious to those skilled in the art. Some of these routes are sketched below



Substituted anilines can be e.g. reacted with the appropriate carboxylic acid chlorides to yield anilides. Moreover, reaction with isocyanates of isothiocyanates may give ureas or thioureas, respectively. Reaction of substituted anilines with chloroformates may yield carbamates (urethanes).

Moreover, substituted arylisocyanates (X = O) or arylisothiocyanates (X = S) may be reacted with primary or secondary aliphatic or aromatic amines to yield ureas or thioureas, respec-

tively. Substituted arylisocyanates (X = O) or arylisothiocyanates (X = S) may also be reacted with aliphatic or aromatic alcohols to yield urethanes (carbamates) or thiocarbamates.

7. Abbreviations: The following frequently used abbreviations are intended to have the following meanings:

AcOH: glacial acetic acid

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane, methylenechloride

DIC: diisopropylcarbodiimide

DMF: N,N-dimethyl formamide

EDC: N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride, "water-soluble carbodiimide"

FMoc: fluorenylmethyloxycarbonyl

NMP: N-Methylpyrrolidone

R: organic radical

TFA: trifluoroacetic acid

THF: tetrahydrofuran

PHARMACOLOGICAL METHODS

The ability of the compounds to interact with potassium channels can be determined by various methods. When patch-clamp techniques (Hamill O.P., Marty A., Nefer E., Sakman B. and Sigworth F.J., *Plügers Arch.* **1981**, *391*, 85-100) are used the ionic current through a single channel of a cell can be recorded.

The activity of the compounds as potassium channel openers can also be measured as relaxation of rat aorta rings according to the following procedure:

A section of rat thoracic aorta between the aortic arch and the diaphragm was dissected out and mounted as ring preparations as described by Taylor P.D. et al., *Brit. J. Pharmacol.* **1994**, *111*, 42-48.

After a 45 min equilibration period under a tension of 2 g, the preparations were contracted to achieve 80% of the maximum response using the required concentration of

phenylephrine. When the phenylephrine response reached a plateau, potential vasodilatory agents were added cumulatively to the bath in small volumes using half log molar increments at 2 min intervals. Relaxation was expressed at the percentage of the contracted tension. The potency of a compound was expressed as the concentration required to evoke a 50% relaxation of the tissue.

In the pancreatic beta-cell the opening of the K_{ATP}-channels can be determined by measuring the subsequent change in the concentration of cytoplasmic free Ca^{2+} concentration according to the method of Arkhammar et al., *J. Biol. Chem.* **1987**, *262*, 5448-5454.

$^{86}Rb^+$ efflux from a beta-cell line

The RIN 5F cell line was grown in RPMI 1640 with Glutamax I, supplemented with 10% fetal calf serum (from GibcoBRL, Scotland, UK) and maintained in an atmosphere of 5% CO_2/ 95% air at 37 °C. The cells were detached with a Trypsin-EDTA solution (from GibcoBRL, Scotland, UK), resuspended in medium, added 1 mCi/mL $^{86}Rb^+$ and replated into microtiter plates (96 well cluster 3596, sterile, from Costar Corporation, MA, USA) at a density of 50000 cells/well in 100 µl/well, and grown 24 hours before use in assay.

The plates were washed four times with Ringer buffer (150 mM NaCl, 10 mM Hepes, 3.0 mM KCl, 1.0 mM $CaCl_2$, 20 mM sucrose, pH 7.1). 80 µL Ringer buffer and 1 µL control- or test compound dissolved in DMSO were added. After incubation for 1 h at room temperature with a lid, 50 µL of the supernatant was transferred to PicoPlates (Packard Instrument Company, CT, USA) and 100 µL MicroScint40 (Packard Instrument Company, CT, USA) was added. The plates were counted in TopCount (Packard Instrument Company, CT, USA) for 1 min/well at the ^{32}P program.

The calculation of EC_{50} and E_{max} was done by SlideWrite (Advanced Graphics Software, Inc., CA, USA) using a four parameter logistic curve: $y = (a-d)/(1+(x/c)^b)+d$, where a = the activity estimated at concentration zero, b = a slope factor, c = the concentration at the middle of the curve and, d = the activity estimated at infinite concentration. EC_{50} = c and E_{max} = d, when the curve is turned off at infinite concentrations.

The compounds according to the invention are effective over a wide dose range. In general satisfactory results are obtained with dosages from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg, per day. A most preferable dosage is about 5 mg to about 200 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceutically acceptable salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Active compound	5.0 mg
Lactosum	67.8 mg Ph.Eur.
Avicel®	31.4 mg
Amberlite®	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

Due to their high degree of activity, the compounds of the invention may be administered to a mammal, especially a human, in need of such treatment, prevention, elimination, alleviation or amelioration of various diseases as mentioned above and especially of diseases of the endocrinological system such as hyperinsulinaemia and diabetes.

The results obtained from screening of the compounds of the present invention show, that some of these are potent potassium channel openers. The most active compounds of this invention show an IC_{50} of 600 nM.

Examples

Example 1. 1-[3,5-Bis-(trifluoromethyl)phenyl]-3-(2,4-dichlorobenzyl)urea

To a solution of 2,4-dichlorobenzylisocyanate (0.22 g, 1.09 mmol) in toluene (4.5 mL) 3,5-bis(trifluoromethyl)aniline (0.16 mL, 1.03 mmol) and triethylamine (0.3 mL) were added and the resulting mixture was heated to 90 °C for 2 h. The mixture was then concentrated and

the residue recrystallized from ethyl acetate (10 mL). 0.15 g (34%) of the title compound was obtained as colourless needles, mp 196-198 °C.

HPLC (254 nm): Elution at 33.98 min, 99.7% pure. LCMS: MH^+ calcd.: 431, found: 431. ^1H NMR (300 MHz, DMSO-d_6): δ = 4.38 (d, J = 7 Hz, 2H), 7.09 (t, J = 7 Hz, 1H), 7.30-7.62 (m, 6H), 8.11 (s, 2H), 9.52 (s, 1H). Anal. Calcd. for $C_{16}H_{10}Cl_2F_6N_2O$ (431.2): C, 44.57; H, 2.34; N, 6.50. Found: C, 44.53; H, 2.34; N, 6.29.

Example 2. Parallel Synthesis of ten N-acylated 3,5-bis(trifluoromethyl)anilines

Into each of ten test tubes with septum a solution of 3,5-bis(trifluoromethyl)aniline (0.078 mL, 0.5 mmol) in pyridine (0.2 mL) and 1,2-dichloroethane (0.5 mL) was placed. Then, while shaking the tubes on a mechanical shaker, to each of the test tubes one acid chloride (0.6 mmol), namely 3-cyanobenzoyl chloride, 2-phenoxypropionyl chloride, butyryl chloride, heptanoyl chloride, pivaloyl chloride, cyclopropanoyl chloride, isobutyryl chloride, 2-ethylhexanoyl chloride, 3-cyclopentylpropionyl chloride and 3-phenylpropionyl chloride, was added with a syringe. The resulting mixtures were shaken for 48 h at room temperature. To each test tube brine (2 mL) and ethyl acetate (2 mL) were added, and after shaking for 5 min the aqueous phases were pipetted off and discarded. The organic layers were washed once with 1N hydrochloric acid (3 mL), once with brine (3 mL) and then dried over magnesium sulfate. The dried ethyl acetate extracts were tranferred into vials and concentrated. Between 156 mg and 63 mg of the corresponding anilides were obtained. Purity and identity of the products was determined by HPLC-MS, and was found to be sufficient for screening.

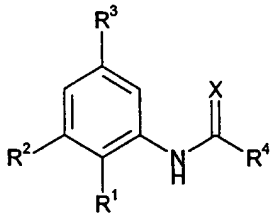
Example 3. Parallel synthesis of 200 substituted aniline derivatives

An array of 200 different aniline derivatives was prepared in the following way:

Into 200 vials 0.1 mmol of 50 different amines was placed. The amines were: isoamylamine, isopropylamine, isobutylamine, neopentylamine, 2,2,2-trifluoroethylamine, propargylamine, dipropylamine, 2-(4-chlorophenyl)ethylamine, 4-methylpiperidine, diisobutylamine, pyrrolidine, 3-(imidazol-1-yl)propylamine, 1,2,3,4-tetrahydroisoquinoline, cis-2,6-dimethylmorpholine, 1-[(3-trifluoromethyl)phenyl]piperazine, azepine, 4-benzoylpiperidine, (3-phenylpropyl)amine, 4-hydroxycyclohexylamine (cis/trans-mixture), trans-3-hydroxycyclohexylamine, 3-hydroxypiperidine, 3-hydroxypyrrolidine, 2-aminoethanol, 3-

aminopropanol, 4-aminobutanol, 6-aminohexanol, 4-(2-aminoethyl)morpholine, 3,3,5-trimethyl-5-aminomethyl-1-cyclohexanol, 1-acetylpiperazine, (2-chlorobenzyl)amine, 2-(ethylamino)ethanol, n-butylamine, 2-methyl-2-amino-1-propanol, cyclohexylmethylamine, 4-(2-aminoethyl)pyridine, 4-(ethylaminomethyl)pyridine, 3-(2-pyridylamino)propylamine, 2-(2-aminoethyl)pyridine, 4-(1-piperidinyl)-4-(aminocarbonyl)piperidine, 1-(pyrrolidin-1-ylcarbonylmethyl)piperazine, 1-(2-furoyl)piperazine, 1-cyclopropyl-1-(4-methoxyphenyl)methylamine, synephrine [N-methyl-2-(4-hydroxyphenyl)-2-hydroxyethylamine; racemic], 2-amino-2-phenylethanol (racemic), norephedrine (1-phenyl-2-aminopropanol), 4-amino-1-benzylpiperidine, 1,2,3,4-tetrahydropapaverine, desipramine and 3-(aminomethyl)pyridine. Then to each of the vials (closed with a septum) 0.25 mL of a mixture of acetonitrile and triethylamine (9:1, vol) was added. Finally solutions of 3,5-bis(trifluoromethyl)phenylisothiocyanate; 3,5-dichlorophenylisothiocyanate, 3,5-bis(trifluoromethyl)phenylisocyanate and 2-chloro-5-(trifluoromethyl)phenylisothiocyanate in acetonitrile (0.6 equivalents) were added to all the vials in such a way that all possible combinations of cyanate/amine were realized. The vials were then shaken for 24 h at room temperature and then concentrated in vacuum. The quality of the compound-array was determined by HPLC-MS of a representative selection of products, and was considered to be sufficient for screening (estimated purity of analyzed samples: 40% to >90%).

Following the procedures described above, the following compounds **I** have been prepared:



I

No	R^1	R^2	R^3	R^4	X	MH^+ expctd	MH^+ found
1	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2CH_3$	O	315	315
2	H	$-CF_3$	$-CF_3$	-NH-(cyclohexyl)	O	355	355
3	H	$-CF_3$	$-CF_3$	$-NH-C(CH_3)_3$	O	328	329
4	H	$-CF_3$	$-CF_3$	$-NH-(4-C_6H_4Cl)$	O	383	383
5	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_3)_2$	O	315	315

6	H	$-CF_3$	$-CF_3$	$-(3-C_6H_4CN)$	O	359	359
7	H	$-CF_3$	$-CF_3$	$-CH(O-Ph)CH_3$	O	378	378
8	H	$-CF_3$	$-CF_3$	$-(CH_2)_2CH_3$	O	300	300
9	H	$-CF_3$	$-CF_3$	$-(CH_2)_5CH_3$	O	342	342
10	H	$-CF_3$	$-CF_3$	$-C(CH_3)_3$	O	314	314
11	H	$-CF_3$	$-CF_3$	cyclopropyl	O	298	298
12	H	$-CF_3$	$-CF_3$	$-CH(CH_3)_2$	O	300	
13	H	$-CF_3$	$-CF_3$	-CH(Et)(n-butyl)	O	356	356
14	H	$-CF_3$	$-CF_3$	$-(CH_2)_2$-(cyclopentyl)	O	354	354
15	H	$-CF_3$	$-CF_3$	$-(CH_2)_2$-Ph	O	362	362
16	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2-CH(CH_3)_2$	S	359	
17	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_3)_2$	S	331	331
18	H	$-CF_3$	$-CF_3$	$-NH-CH_2-CH(CH_3)_2$	S	345	
19	H	$-CF_3$	$-CF_3$	$-NH-CH_2-C(CH_3)_3$	S	359	359
20	H	$-CF_3$	$-CF_3$	$-NH-CH_2-CF_3$	S	371	
21	H	$-CF_3$	$-CF_3$	$-NH-CH_2-CCH$	S	327	
22	H	$-CF_3$	$-CF_3$	$-N[(CH_2)_2CH_3]_2$	S	373	
23	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2-(4-C_6H_4Cl)$	S	427	
24	H	$-CF_3$	$-CF_3$	(4-methyl)piperidin-1-yl	S	371	
25	H	$-CF_3$	$-CF_3$	$-N[CH_2-CH(CH_3)_2]_2$	S	401	
26	H	$-CF_3$	$-CF_3$	pyrrolidin-1-yl	S	343	
27	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3$-(imidazol-1-yl)	S	397	
28	H	$-CF_3$	$-CF_3$	1,2,3,4-tetrahydroisoquinolin-2-yl	S	405	
29	H	$-CF_3$	$-CF_3$	(2,6-dimethyl)morpholin-4-yl	S	387	
30	H	$-CF_3$	$-CF_3$	4-[(3-trifluoromethyl)phenyl]piperazin-1-yl	S	502	
31	H	$-CF_3$	$-CF_3$	azepin-1-yl	S	371	
32	H	$-CF_3$	$-CF_3$	(4-benzoyl)piperidin-1-yl	S	461	
33	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3$-Ph	S	407	
34	H	$-CF_3$	$-CF_3$	-NH-(4-hydroxycyclohexyl)	S	387	
35	H	$-CF_3$	$-CF_3$	-NH-(3-hydroxycyclohexyl)	S	387	
36	H	$-CF_3$	$-CF_3$	4-hydroxypiperidin-1-yl	S	373	
37	H	$-CF_3$	$-CF_3$	3-hydroxypiperidin-1-yl	S	373	
38	H	$-CF_3$	$-CF_3$	3-hydroxypyrrolidin-1-yl	S	359	
39	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2-OH$	S	333	
40	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-OH$	S	347	
41	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_4-OH$	S	361	
42	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_6-OH$	S	389	

43	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(morpholin-4-yl)	S	402	
44	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl	S	443	
45	H	$-CF_3$	$-CF_3$	(4-acetyl)piperazin-1-yl	S	400	
46	H	$-CF_3$	$-CF_3$	$-NH-CH_2-(2-C_6H_4Cl)$	S	413	
47	H	$-CF_3$	$-CF_3$	$-N(Et)-(CH_2)_2-OH$	S	361	
48	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-CH_3$	S	345	
49	H	$-CF_3$	$-CF_3$	$-NH-C(CH_3)_2-CH_2-OH$	S	361	361
50	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(cyclohexyl)	S	385	
51	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(4-pyridyl)	S	394	
52	H	$-CF_3$	$-CF_3$	$-N(Et)-CH_2$-(4-pyridyl)	S	408	408
53	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-NH$-(2-pyridyl)	S	423	423
54	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(2-pyridyl)	S	394	
55	H	$-CF_3$	$-CF_3$	[4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl	S	483	483
56	H	$-CF_3$	$-CF_3$	4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl	S	469	
57	H	$-CF_3$	$-CF_3$	4-(2-furoyl)piperazin-1-yl	S	452	
58	H	$-CF_3$	$-CF_3$	$-NH-CH$(cyclopropyl)$(4-C_6H_4-OCH_3)$	S	449	
59	H	$-CF_3$	$-CF_3$	$-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$	S	439	439
60	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_2-OH)$-Ph	S	409	
61	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_3)-CH(OH)$-Ph	S	423	423
62	H	$-CF_3$	$-CF_3$	-NH-(1-benzylpiperidin-4-yl)	S	462	
63	H	$-CF_3$	$-CF_3$	1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl	S	615	615
64	H	$-CF_3$	$-CF_3$	$-N(CH_3)-(CH_2)_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)	S	538	
65	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(3-pyridyl)	S	380	
66	H	-Cl	-Cl	$-NH-(CH_2)_2-CH(CH_3)_2$	S	292	
67	H	-Cl	-Cl	$-NH-CH(CH_3)_2$	S	264	
68	H	-Cl	-Cl	$-NH-CH_2-CH(CH_3)_2$	S	278	
69	H	-Cl	-Cl	$-NH-CH_2-C(CH_3)_3$	S	292	291
70	H	-Cl	-Cl	$-NH-CH_2-CF_3$	S	304	
71	H	-Cl	-Cl	$-NH-CH_2-CCH$	S	260	
72	H	-Cl	-Cl	$-N[(CH_2)_2CH_3]_2$	S	306	
73	H	-Cl	-Cl	$-NH-(CH_2)_2-(4-C_6H_4Cl)$	S	360	
74	H	-Cl	-Cl	(4-methyl)piperidin-1-yl	S	304	
75	H	-Cl	-Cl	$-N[CH_2-CH(CH_3)_2]_2$	S	334	
76	H	-Cl	-Cl	pyrrolidin-1-yl	S	276	

77	H	-Cl	-Cl	-NH-$(CH_2)_3$-(imidazol-1-yl)	S	330
78	H	-Cl	-Cl	1,2,3,4-tetrahydroisoquinolin-2-yl	S	338
79	H	-Cl	-Cl	(2,6-dimethyl)morpholin-4-yl	S	320
80	H	-Cl	-Cl	4-[(3-trifluoromethyl)phenyl]piperazin-1-yl	S	435
81	H	-Cl	-Cl	azepin-1-yl	S	304
82	H	-Cl	-Cl	(4-benzoyl)piperidin-1-yl	S	394
83	H	-Cl	-Cl	-NH-$(CH_2)_3$-Ph	S	340
84	H	-Cl	-Cl	-NH-(4-hydroxycyclohexyl)	S	320
85	H	-Cl	-Cl	-NH-(3-hydroxycyclohexyl)	S	320
86	H	-Cl	-Cl	4-hydroxypiperidin-1-yl	S	306
87	H	-Cl	-Cl	3-hydroxypiperidin-1-yl	S	306
88	H	-Cl	-Cl	3-hydroxypyrrolidin-1-yl	S	292
89	H	-Cl	-Cl	-NH-$(CH_2)_2$-OH	S	266
90	H	-Cl	-Cl	-NH-$(CH_2)_3$-OH	S	280
91	H	-Cl	-Cl	-NH-$(CH_2)_4$-OH	S	294
92	H	-Cl	-Cl	-NH-$(CH_2)_6$-OH	S	322
93	H	-Cl	-Cl	-NH-$(CH_2)_2$-(morpholin-4-yl)	S	335
94	H	-Cl	-Cl	-NH-CH_2-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl	S	376
95	H	-Cl	-Cl	(4-acetyl)piperazin-1-yl	S	333
96	H	-Cl	-Cl	-NH-CH_2-(2-C_6H_4Cl)	S	346
97	H	-Cl	-Cl	-N(Et)-$(CH_2)_2$-OH	S	294
98	H	-Cl	-Cl	-NH-$(CH_2)_3$-CH_3	S	278
99	H	-Cl	-Cl	-NH-$C(CH_3)_2$-CH_2-OH	S	294
100	H	-Cl	-Cl	-NH-CH_2-(cyclohexyl)	S	318
101	H	-Cl	-Cl	-NH-$(CH_2)_2$-(4-pyridyl)	S	327
102	H	-Cl	-Cl	-N(Et)-CH_2-(4-pyridyl)	S	341
103	H	-Cl	-Cl	-NH-$(CH_2)_3$-NH-(2-pyridyl)	S	356
104	H	-Cl	-Cl	-NH-$(CH_2)_2$-(2-pyridyl)	S	327
105	H	-Cl	-Cl	[4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl	S	416
106	H	-Cl	-Cl	4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl	S	402
107	H	-Cl	-Cl	4-(2-furoyl)piperazin-1-yl	S	385
108	H	-Cl	-Cl	-NH-CH(cyclopropyl)(4-C_6H_4-OCH_3)	S	382
109	H	-Cl	-Cl	-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)	S	372
110	H	-Cl	-Cl	-NH-CH(CH_2-OH)-Ph	S	342
111	H	-Cl	-Cl	-NH-CH(CH_3)-CH(OH)-Ph	S	356
112	H	-Cl	-Cl	-NH-(1-benzylpiperidin-4-yl)	S	395

113	H	-Cl	-Cl	1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl	S	548	
114	H	-Cl	-Cl	-N(CH_3)-(CH_2)$_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)	S	471	
115	H	-Cl	-Cl	-NH-CH_2-(3-pyridyl)	S	313	
116	H	-CF_3	-CF_3	-NH-(CH_2)$_2$-CH(CH_3)$_2$	O	343	
117	H	-CF_3	-CF_3	-NH-CH(CH_3)$_2$	O	315	
118	H	-CF_3	-CF_3	-NH-CH_2-CH(CH_3)$_2$	O	329	
119	H	-CF_3	-CF_3	-NH-CH_2-C(CH_3)$_3$	O	343	343
120	H	-CF_3	-CF_3	-NH-CH_2-CF_3	O	355	355
121	H	-CF_3	-CF_3	-NH-CH_2-CCH	O	311	
122	H	-CF_3	-CF_3	-N[(CH_2)$_2$$CH_3$]$_2$	O	357	
123	H	-CF_3	-CF_3	-NH-(CH_2)$_2$-(4-C_6H_4Cl)	O	411	
124	H	-CF_3	-CF_3	(4-methyl)piperidin-1-yl	O	355	
125	H	-CF_3	-CF_3	-N[CH_2-CH(CH_3)$_2$]$_2$	O	385	
126	H	-CF_3	-CF_3	pyrrolidin-1-yl	O	327	
127	H	-CF_3	-CF_3	-NH-(CH_2)$_3$-(imidazol-1-yl)	O	381	
128	H	-CF_3	-CF_3	1,2,3,4-tetrahydroisoquinolin-2-yl	O	389	
129	H	-CF_3	-CF_3	(2,6-dimethyl)morpholin-4-yl	O	371	
130	H	-CF_3	-CF_3	4-[(3-trifluoromethyl)phenyl]piperazin-1-yl	O	486	
131	H	-CF_3	-CF_3	azepin-1-yl	O	355	
132	H	-CF_3	-CF_3	(4-benzoyl)piperidin-1-yl	O	445	
133	H	-CF_3	-CF_3	-NH-(CH_2)$_3$-Ph	O	391	
134	H	-CF_3	-CF_3	-NH-(4-hydroxycyclohexyl)	O	371	371
135	H	-CF_3	-CF_3	-NH-(3-hydroxycyclohexyl)	O	371	
136	H	-CF_3	-CF_3	4-hydroxypiperidin-1-yl	O	357	
137	H	-CF_3	-CF_3	3-hydroxypiperidin-1-yl	O	357	
138	H	-CF_3	-CF_3	3-hydroxypyrrolidin-1-yl	O	343	343
139	H	-CF_3	-CF_3	-NH-(CH_2)$_2$-OH	O	317	
140	H	-CF_3	-CF_3	-NH-(CH_2)$_3$-OH	O	331	331
141	H	-CF_3	-CF_3	-NH-(CH_2)$_4$-OH	O	345	
142	H	-CF_3	-CF_3	-NH-(CH_2)$_6$-OH	O	373	
143	H	-CF_3	-CF_3	-NH-(CH_2)$_2$-(morpholin-4-yl)	O	386	
144	H	-CF_3	-CF_3	-NH-CH_2-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl	O	427	
145	H	-CF_3	-CF_3	(4-acetyl)piperazin-1-yl	O	384	
146	H	-CF_3	-CF_3	-NH-CH_2-(2-C_6H_4Cl)	O	397	

147	H	$-CF_3$	$-CF_3$	$-N(Et)-(CH_2)_2-OH$	O	345	
148	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-CH_3$	O	329	
149	H	$-CF_3$	$-CF_3$	$-NH-C(CH_3)_2-CH_2-OH$	O	345	
150	H	$-CF_3$	$-CF_3$	$-NH-CH_2-$(cyclohexyl)	O	369	
151	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2-$(4-pyridyl)	O	378	
152	H	$-CF_3$	$-CF_3$	$-N(Et)-CH_2-$(4-pyridyl)	O	392	
153	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-NH-$(2-pyridyl)	O	407	
154	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2-$(2-pyridyl)	O	378	
155	H	$-CF_3$	$-CF_3$	[4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl	O	467	
156	H	$-CF_3$	$-CF_3$	4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl	O	453	
157	H	$-CF_3$	$-CF_3$	4-(2-furoyl)piperazin-1-yl	O	436	
158	H	$-CF_3$	$-CF_3$	$-NH-CH($cyclopropyl$)(4-C_6H_4-OCH_3)$	O	433	433
159	H	$-CF_3$	$-CF_3$	$-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$	O	423	
160	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_2-OH)-Ph$	O	393	
161	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_3)-CH(OH)-Ph$	O	407	
162	H	$-CF_3$	$-CF_3$	-NH-(1-benzylpiperidin-4-yl)	O	446	
163	H	$-CF_3$	$-CF_3$	1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl	O	599	
164	H	$-CF_3$	$-CF_3$	$-N(CH_3)-(CH_2)_3-$(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)	O	522	
165	H	$-CF_3$	$-CF_3$	$-NH-CH_2-$(3-pyridyl)	O	364	
166	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-CH(CH_3)_2$	S	325	
167	-Cl	H	$-CF_3$	$-NH-CH(CH_3)_2$	S	297	
168	-Cl	H	$-CF_3$	$-NH-CH_2-CH(CH_3)_2$	S	311	
169	-Cl	H	$-CF_3$	$-NH-CH_2-C(CH_3)_3$	S	325	325
170	-Cl	H	$-CF_3$	$-NH-CH_2-CF_3$	S	337	
171	-Cl	H	$-CF_3$	$-NH-CH_2-CCH$	S	293	
172	-Cl	H	$-CF_3$	$-N[(CH_2)_2CH_3]_2$	S	339	339
173	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-(4-C_6H_4Cl)$	S	394	
174	-Cl	H	$-CF_3$	(4-methyl)piperidin-1-yl	S	337	337
175	-Cl	H	$-CF_3$	$-N[CH_2-CH(CH_3)_2]_2$	S	367	
176	-Cl	H	$-CF_3$	pyrrolidin-1-yl	S	309	
177	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-$(imidazol-1-yl)	S	363	
178	-Cl	H	$-CF_3$	1,2,3,4-tetrahydroisoquinolin-2-yl	S	371	
179	-Cl	H	$-CF_3$	(2,6-dimethyl)morpholin-4-yl	S	353	
180	-Cl	H	$-CF_3$	4-[(3-trifluoromethyl)phenyl]piperazin-1-yl	S	468	
181	-Cl	H	$-CF_3$	azepin-1-yl	S	337	

182	-Cl	H	$-CF_3$	(4-benzoyl)piperidin-1-yl	S	427	
183	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-Ph$	S	373	
184	-Cl	H	$-CF_3$	-NH-(4-hydroxycyclohexyl)	S	353	
185	-Cl	H	$-CF_3$	-NH-(3-hydroxycyclohexyl)	S	353	
186	-Cl	H	$-CF_3$	4-hydroxypiperidin-1-yl	S	339	
187	-Cl	H	$-CF_3$	3-hydroxypiperidin-1-yl	S	339	
188	-Cl	H	$-CF_3$	3-hydroxypyrrolidin-1-yl	S	325	
189	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-OH$	S	299	
190	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-OH$	S	313	
191	-Cl	H	$-CF_3$	$-NH-(CH_2)_4-OH$	S	327	
192	-Cl	H	$-CF_3$	$-NH-(CH_2)_6-OH$	S	355	
193	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-$(morpholin-4-yl)	S	368	
194	-Cl	H	$-CF_3$	$-NH-CH_2-$(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl	S	409	
195	-Cl	H	$-CF_3$	(4-acetyl)piperazin-1-yl	S	366	
196	-Cl	H	$-CF_3$	$-NH-CH_2-(2-C_6H_4Cl)$	S	380	
197	-Cl	H	$-CF_3$	$-N(Et)-(CH_2)_2-OH$	S	327	
198	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-CH_3$	S	311	
199	-Cl	H	$-CF_3$	$-NH-C(CH_3)_2-CH_2-OH$	S	327	
200	-Cl	H	$-CF_3$	$-NH-CH_2-$(cyclohexyl)	S	351	
201	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-$(4-pyridyl)	S	360	
202	-Cl	H	$-CF_3$	$-N(Et)-CH_2-$(4-pyridyl)	S	374	
203	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-NH-$(2-pyridyl)	S	389	388
204	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-$(2-pyridyl)	S	360	
205	-Cl	H	$-CF_3$	[4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl	S	449	
206	-Cl	H	$-CF_3$	4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl	S	435	
207	-Cl	H	$-CF_3$	4-(2-furoyl)piperazin-1-yl	S	418	
208	-Cl	H	$-CF_3$	$-NH-CH($cyclopropyl$)(4-C_6H_4-OCH_3)$	S	415	
209	-Cl	H	$-CF_3$	$-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$	S	405	
210	-Cl	H	$-CF_3$	$-NH-CH(CH_2-OH)-Ph$	S	375	375
211	-Cl	H	$-CF_3$	$-NH-CH(CH_3)-CH(OH)-Ph$	S	389	
212	-Cl	H	$-CF_3$	-NH-(1-benzylpiperidin-4-yl)	S	428	
213	-Cl	H	$-CF_3$	1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl	S	582	
214	-Cl	H	$-CF_3$	$-N(CH_3)-(CH_2)_3-$(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)	S	505	
215	-Cl	H	$-CF_3$	$-NH-CH_2-$(3-pyridyl)	S	346	346

216	H	$-CF_3$	$-CF_3$	$-NH-CH_2-(2,4-C_6H_3Cl_2)$	O	432	432

Example 4. General synthetic pathway to 1-aryl-3-alkylthioureas

A solution of the appropriately substituted aniline (8 mmol) and thiocarbonyldiimidazole (1.43 g ; 8 mmol) in dioxane (30 mL) was heated at 50°C for 48-72 h (until disappearance of the aniline from the reaction mixture monitored by TLC). The appropriate alkylamine (or cycloalkylalkylamine) (8 mmol) was added to the reaction medium and the resulting solution was heated at 60°C for 4-12 h. The solvent was removed by distillation under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with 4N HCl (50 mL), then with water (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated to dryness. The residue was dissolved in a small volume of ethanol (5-10 mL). The solution was supplemented with 2N HCl (100 mL) and the resulting precipitate was collected by filtration, washed with water and dried (yields : 20-60%).

The following compounds have been obtained :

1-Cyclohexylmethyl-3-(3,5-dichlorophenyl)thiourea
mp 134-135°C. IR (KBr) : 3261, 3079, 2922, 2850, 1552, 1445, 1337, 1248 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}Cl_2N_2S$ (317.28) : C, 53.00 ; H, 5.72 ; N, 8.83 ; S, 10.11. Found : C, 53.13 ; H, 6.10 ; N, 9.00 ; S, 10.38.

1-Cyclohexylmethyl-3-(3,5-difluorophenyl)thiourea
mp 125-127°C. IR (KBr) : 3318, 3201, 2924, 2854, 1626, 1611, 1565, 1536, 1477, 1262, 1252, 1122 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}F_2N_2S$ (284.37) : C, 59.13 ; H, 6.38 ; N, 9.85 ; S, 11.28. Found : C, 59.33 ; H, 6.49 ; N, 10.22 ; S, 11.01.

1-Cyclohexylmethyl-3-(2,5-difluorophenyl)thiourea

mp 89-91°C. IR (KBr) : 3316, 3168, 2922, 2850, 1553, 1500, 1250, 1212, 1196, 1184 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}F_2N_2S$ (284.37) : C, 59.13 ; H, 6.38 ; N, 9.85 ; S, 11.28. Found : C, 59.20 ; H, 6.63 ; N, 10.22 ; S, 11.33.

(R)-1-(1-Cyclohexylethyl)-3-(3,5-difluorophenyl)thiourea
mp 121-123°C. IR (KBr) : 3315, 3200, 3043, 2924, 2852, 1625, 1612, 1570, 1525, 1477, 1254, 1120 cm^{-1}. Anal. Calcd. for $C_{15}H_{20}F_2N_2S$ (298.40) : C, 60.38 ; H, 6.75 ; N, 9.39 ; S, 10.75. Found : C, 60.23 ; H, 6.92 ; N, 9.46 ; S, 11.05.

Example 5 Heptanoic acid (3,5-bis(trifluoromethyl)phenyl)amide

To a solution of heptanoyl chloride (0.186 ml, 1.1 mmol) in diethyl ether (1 ml) 3,5-bis-(trifluoromethyl)aniline (0.196 ml, 1.3 mmol) was added dropwise. After stirring for 2 h, the precipitate was filtered off and washed with diethyl ether. The filtrate was concentrated to give a sirup, which was purified by flash chromatography using ethyl acetate/heptane 1:4 and 1:2 to give the title compound as oily crystals. Yield 0.65 g (83%). The product could be recrystalised from ethanol/water to give oily crystals contaminated with heptanoic chloride (3.67 mol%). MA. Calculated for $C_{15}H_{17}NOF_6.0.1C_7H_{13}ClO$: C 53.22%; H 5.23%; N 3.95% Found: C 53.31%; H 5.10%; N 4.06%. EI SP/MS: 341 (M+). ^{1}H-NMR (DMSO): δ 10.55 (s, 1H, NH); 8.27 (s, 2H); 7.70 (s, 1H); 2.35 (t, 2H); 1.60 (p, 2H); 1.3 (m, 6H); 0.88 ppm (t, 3H).

Example 6 N-(3,5-Bis(trifluoromethyl)phenyl)-2-phenoxypropionamide

To a solution of 2-phenoxypropionyl chloride (0.22 g, 1.1 mmol) in diethyl ether (4 ml) 3,5-bis-(trifluoromethyl)aniline (0.200 ml, 1.3 mmol) was added. After stirring for 2.5 h the reaction mixture was filtered and the filtrate concentrated to give a sirup, which was crystalised from toluene to give the title compound as white crystals. Yield 0.321 g (75%).mp 113.5-114.5°C. MA. Calculated for $C_{17}H_{13}NO_2F_6$: C 54.12%; H 3.47%; N 3.71% Found: C 54.21%; H 3.49%; N 3.68%. EI SP/MS: 377 (M+). ^{1}H-NMR (DMSO): δ 10.80 (s, 1H, NH); 8.39 (s, 2H); 7.80 (s, 1H); 7.3 (m, 2H); 6.95 (m, 3H); 4.94 (q, 1H); 1.57 ppm (d, 3H).

Example 7 1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-chlorophenyl)urea

4-Chlorophenylisocyanate (0.175 ml, 1.36 mmol) was added to 3,5-bis-(trifluoromethyl)aniline (0.233 ml, 1.5 mmol) and stirred for 1 h. The almost solid reaction mixture was recrystalised first from ethyl acetate and then from toluene to give the title compound. Yield 0.315g (61%). Mp 224.5-225.0°C. EI SP/MS: 382 (M+).
1H-NMR (DMSO): δ 9.42 (br s, 1H, NH); 9.13 (br s, 1H, NH); 8.12 (s, 2H); 7.63 (s, 1H); 7.50 (d, 2H); 7.35 ppm (d, 2H).

Example 8 N-(3,5-Bis(trifluoromethyl)phenyl)-3-phenylacrylamide

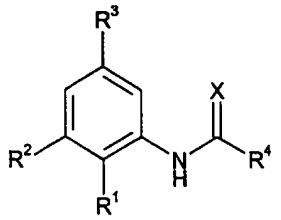
The title compound was prepared from 3,5-bis(trifluoromethyl)aniline and cinnamoyl chloride by a method analogous to the one described in Example 2; LC-MS: m/e 360 (M^+ +1).

Example 9 2-Phenylcyclopropanecarboxylic acid (3,5-bis(trifluoromethyl)phenyl)-amide

The title compound was prepared from 3,5-bis(trifluoromethyl)aniline and 2-phenylcyclopropanecarboxylic acid chloride by a method analogous to the one described in Example 2; LC-MS: m/e 374 (M^+ +1).

CLAIMS

1. A compound of the general formula I



I

wherein

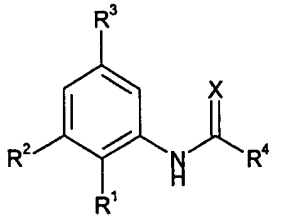
R^1 and R^2 are independently hydrogen, trifluoromethyl or halogen, with the provisio that R^1 and R^2 are not simultaneously hydrogen;

R^3 is trifluoromethyl or halogen;

R^4 is straight or branched alkyl optionally substituted with C_{3-8}-cycloalkyl, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl, or
R^4 is Y-R^5, Y being -O- or -N(R^6)- and R^5 and R^6 being independently straight or branched alkyl optionally substituted with C_{3-8}-cycloalkyl, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl;
or R^5 and R^6 are linked to each other forming a 3-8 membered ring;

X is O or S;
or a pharmaceutically acceptable salts thereof.

2. A compound of the general formula I



I

wherein

R^1 is hydrogen, trifluoromethyl or halogen;

R^2 is hydrogen, trifluoromethyl or halogen;

R^3 is trifluoromethyl or halogen;

R^4 is straight or branched alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl, optionally substituted with C_{3-8}-cycloalkyl or aryloxy; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl optionally substituted with halogen, cyano or trifluoromethyl; or
aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or
Y-R^5, wherein Y is -O- or -N(R^6)-
wherein R^5 is straight or branched alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl, optionally substituted with C_{3-8}-cycloalkyl, imidazolyl, methoxyphenyl or 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl, optionally substituted with halogen, cyano, benzyl or trifluoromethyl; or
aryloxy, optionally substituted with halogen, cyano or trifluoromethyl;
R^6 is hydrogen; or
straight or branched alkyl optionally substituted with C_{3-8}-cycloalkyl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl, optionally substituted with halogen, cyano or trifluoromethyl; or
aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or

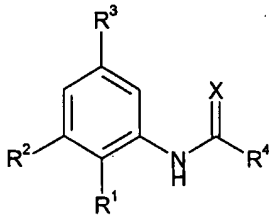
R^5 and R^6 are linked to form a 3-8 membered ring which is optionally substituted with straight or branched alkyl or pyrrolidinylcarbonylmethyl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
furoyl, benzoyl, acetyl, hydroxy, aminocarbonyl; or
piperidinyl; or
R^5 and R^6 are linked to form a saturated or unsaturated isoquinolin ring, optionally substituted with methoxy or dimethoxybenzyl;

X is O or S;

or a pharmaceutically acceptable salts thereof.

with the proviso that R^1 and R^2 are not both hydrogen at the same time;

3. A compound of the general formula I



I

wherein

R^1 is hydrogen, trifluoromethyl or halogen;

R^2 is hydrogen, trifluoromethyl or halogen;

R^3 is trifluoromethyl or halogen;

R^4 is straight or branched alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl, optionally substituted with C_{3-8}-cycloalkyl or aryloxy; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl optionally substituted with halogen, cyano or trifluoromethyl; or
aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or
Y-R^5, wherein Y is -O- or -N(R^6)-
wherein R^5 is straight or branched alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl, optionally substituted with C_{3-8}-cycloalkyl, imidazolyl, methoxyphenyl or 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl;
heterocyclyl, optionally substituted with halogen, cyano, benzyl or trifluoromethyl; or
aryloxy, optionally substituted with halogen, cyano or trifluoromethyl;

R^6 is hydrogen; or
straight or branched alkyl optionally substituted with C_{3-8}-cycloalkyl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl, optionally substituted with halogen, cyano or trifluoromethyl; or
aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or

R^5 and R^6 are linked to form a 3-8 membered ring which is optionally substituted with straight or branched alkyl, optionally substituted with pyrrolidinylcarbonylmethyl (??); or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
furoyl, benzoyl, acetyl, hydroxy, aminocarbonyl; or
piperidinyl; or
R^5 and R^6 are linked to form a saturated or unsaturated isoquinolin ring, optionally substituted with methoxy or dimethoxybenzyl;

X is O or S;

or a pharmaceutically acceptable salts thereof.

with the proviso that R^1 and R^2 are not both hydrogen at the same time;

and further provided that:

when R^2 is hydrogen and R^1 and R^3 are chloro, then
R^4 can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
R^4 can not be methyl, unsubstituted or monosubstituted with aryl, aryloxy, alkylamino, arylamino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium or aminoalkyl;
R^4 can not be n-alkyl;
R^4 can not be $-(CH_2)_3-OAr$;
R^4 can not be 2,6-dimethylpiperidin-1-yl, methylamino, butylamino, benzylamino, arylamino, dimethylamino, diethylamino, dipropylamino, dibenzylamino, (methyl)(propargyl)amino, (1-phenylcyclohex-1-yl)methylamino, 4-heteroarylpiperazin-1-yl, (6-methylpyridin-2-yl)methylamino, (4-pyridinylmethyl)(methyl)amino or 2,5-dimethylpyrrolidin-1-yl;
and further provided that:

when R^2 is hydrogen and R^1 and R^3 are trifluoromethyl, then
R^4 can not be methyl, pyridyl, ethyl, n-propyl or 2-propylbutyl;
and further provided that:

when R^1 is hydrogen and R^2 and R^3 are chloro, then
R^4 can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
R^4 can not be methyl, unsubstituted or monosubstituted with aryl, aryloxy, alkylamino, arylamino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium or aminoalkyl;
R^4 can not be n-alkyl, cyclopropyl or 2-propylbutyl;
R^4 can not be $-(CH_2)_3-OAr$ or $-CH(OH)CH_3$;
R^4 can not be arylamino, methylamino, isobutylamino, butylamino, 3-hydroxypropylamino, dimethylamino, [1-methyl-1-(4-bromophenyl)ethyl]amino, (methyl)(propargyl)amino, (isopropyl)(propargyl)amino, di(n-butyl)amino, dibenzylamino or (benzyl)(n-butyl)amino;
and further provided that:

when X is oxygen, R^1 is hydrogen and R^2 and R^3 are trifluoromethyl, then
R^4 can not be heterocyclyl;
R^4 can not be methyl, unsubstituted or monosubstituted with heteroaryloxy, ammonium, acyl, 1-oximoalkyl, heterocyclyl or 1-iminoalkyl;
R^4 can not be 2-propylbutyl or cyclopropyl;
R^4 can not be benzylamino, 2-phenylethylamino, (1-phenyl)ethylamino, 4-chlorobenzylamino, 2-chlorobenzylamino, 2-(4-chlorophenyl)ethylamino, 3,4-dichlorobenzylamino, (3,4-dichlorobenzyl)(methyl)amino, (2-ethylhex-1-yl)amino, isopropylamino, propylamino, butylamino or 4-methyl-1-piperazinyl;
and further provided that:

when X is sulfur, R^1 is hydrogen and R^2 and R^3 are trifluoromethyl, then
R^4 can not be benzylamino, 3,4-dimethylbenzylamino, 4-methoxybenzylamino, 3,4-dichlorobenzylamino, (2-hydroxy-1-methyl-2-phenylethyl)(methyl)amino, isopropylamino, n-propylamino, n-pentylamino, 4-chlorobenzylamino, 1-piperidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, 2,6-dimethyl-4-thiomorpholinyl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl or 4-ethoxycarbonylpiperazin-1-yl;

and further provided that:

when R^1 is chloro, R^2 is hydrogen and R^3 is trifluoromethyl, then
R^4 can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
R^4 can not be methyl, unsubstituted or substituted with aryl, heteroaryl, aryloxy, amino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium, aminoalkyl;
R^4 can not be unsubstituted n-alkyl, cyclopropyl, isopropyl, isobutyl, benzyl, 2-ethylpropyl, 2-propylbutyl;
R^4 can not be diisopropylamino, 2,6-dimethylpiperidin-1-yl, methylamino, dimethylamino, (1,1-dimethylpropargyl)amino, ethylamino, butylamino, (2-hydroxyprop-1-yl)amino or 1-adamantylamino.

4. A compound according to claim1, 2 or 3, wherein R^1 is hydrogen and R^2 and R^3 are trifluoromethyl.

5. A compound according to claim 1, 2 or 3, wherein R^1 is hydrogen and R^2 and R^3 are chloro.

6. A compound according to claim 1, 2 or 3, wherein R^1 is hydrogen and R^2 and R^3 are fluoro.

7. A compound according to claim 1, 2 or 3, wherein R^2 is hydrogen and R^1 and R^3 are fluoro.

8. A compound according to claim 1, 2 or 3, wherein R^2 is hydrogen, R^1 is chloro and R^3 is trifluoromethyl.

9. A compound according to any of the preceding claims, wherein X = O and R^4 = -NH-R^5, R^5 being lower straight or branched alkyl, optionally substituted with C_{3-8}-cycloalkyl, halogen, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl.

10. A compound according to any of the preceding claims, wherein X = S and R^4 = -NH-R^5, R^5 being lower straight or branched alkyl, optionally substituted with C_{3-8}-cycloalkyl, halogen, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl.

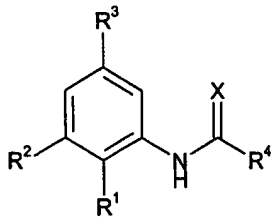
11. A compound according to any of the preceding claims, wherein X = O and R^4 is lower straight or branched alkyl, optionally substituted with C_{3-8}-cycloalkyl, halogen, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl.

12. A compound according to claim wherein X is S and R^4 is N-R^5 wherein R^5 is alkyl substituted with cyclohexyl.

13. A compound according to claim 4 wherein X is O and R^4 is alkyl, phenyl substituted with chloro or O-R^5, wherein R^5 is phenyl.

14. A compound selected from the group consisting of
1-[3,5-Bis-(trifluoromethyl)phenyl]-3-(2,4-dichlorobenzyl)urea
1-Cyclohexylmethyl-3-(3,5-dichlorophenyl)thiourea
1-Cyclohexylmethyl-3-(3,5-difluorophenyl)thiourea
1-Cyclohexylmethyl-3-(2,5-difluorophenyl)thiourea
(R)-1-(1-Cyclohexylethyl)-3-(3,5-difluorophenyl)thiourea
Heptanoic acid (3,5-bis(trifluoromethyl)phenyl)amide
N-(3,5-Bis(trifluoromethyl)phenyl)-2-phenoxypropionamide
1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-chlorophenyl)urea
N-(3,5-Bis(trifluoromethyl)phenyl)-3-phenylacrylamide or
2-Phenylcyclopropanecarboxylic acid (3,5-bis(trifluoromethyl)phenyl)-amide.

15. A compound of formula I selected from the group consisting of:



I

No	R^1	R^2	R^3	R^4	X
1	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2CH_3$	O
2	H	$-CF_3$	$-CF_3$	-NH-(cyclohexyl)	O
3	H	$-CF_3$	$-CF_3$	$-NH-C(CH_3)_3$	O
4	H	$-CF_3$	$-CF_3$	$-NH-(4-C_6H_4Cl)$	O
5	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_3)_2$	O
6	H	$-CF_3$	$-CF_3$	$-(3-C_6H_4CN)$	O
7	H	$-CF_3$	$-CF_3$	$-CH(O-Ph)CH_3$	O
8	H	$-CF_3$	$-CF_3$	$-(CH_2)_2CH_3$	O
9	H	$-CF_3$	$-CF_3$	$-(CH_2)_5CH_3$	O
10	H	$-CF_3$	$-CF_3$	$-C(CH_3)_3$	O
11	H	$-CF_3$	$-CF_3$	cyclopropyl	O
12	H	$-CF_3$	$-CF_3$	$-CH(CH_3)_2$	O
13	H	$-CF_3$	$-CF_3$	-CH(Et)(n-butyl)	O
14	H	$-CF_3$	$-CF_3$	$-(CH_2)_2$-(cyclopentyl)	O
15	H	$-CF_3$	$-CF_3$	$-(CH_2)_2$-Ph	O
16	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2-CH(CH_3)_2$	S
17	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_3)_2$	S
18	H	$-CF_3$	$-CF_3$	$-NH-CH_2-CH(CH_3)_2$	S
19	H	$-CF_3$	$-CF_3$	$-NH-CH_2-C(CH_3)_3$	S
20	H	$-CF_3$	$-CF_3$	$-NH-CH_2-CF_3$	S
21	H	$-CF_3$	$-CF_3$	$-NH-CH_2-CCH$	S
22	H	$-CF_3$	$-CF_3$	$-N[(CH_2)_2CH_3]_2$	S
23	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2-(4-C_6H_4Cl)$	S
24	H	$-CF_3$	$-CF_3$	(4-methyl)piperidin-1-yl	S
25	H	$-CF_3$	$-CF_3$	$-N[CH_2-CH(CH_3)_2]_2$	S
26	H	$-CF_3$	$-CF_3$	pyrrolidin-1-yl	S
27	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3$-(imidazol-1-yl)	S
28	H	$-CF_3$	$-CF_3$	1,2,3,4-tetrahydroisoquinolin-2-yl	S
29	H	$-CF_3$	$-CF_3$	(2,6-dimethyl)morpholin-4-yl	S
30	H	$-CF_3$	$-CF_3$	4-[(3-trifluoromethyl)phenyl]piperazin-1-yl	S
31	H	$-CF_3$	$-CF_3$	azepin-1-yl	S
32	H	$-CF_3$	$-CF_3$	(4-benzoyl)piperidin-1-yl	S
33	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3$-Ph	S

34	H	$-CF_3$	$-CF_3$	-NH-(4-hydroxycyclohexyl)	S
35	H	$-CF_3$	$-CF_3$	-NH-(3-hydroxycyclohexyl)	S
36	H	$-CF_3$	$-CF_3$	4-hydroxypiperidin-1-yl	S
37	H	$-CF_3$	$-CF_3$	3-hydroxypiperidin-1-yl	S
38	H	$-CF_3$	$-CF_3$	3-hydroxypyrrolidin-1-yl	S
39	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2-OH$	S
40	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-OH$	S
41	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_4-OH$	S
42	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_6-OH$	S
43	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(morpholin-4-yl)	S
44	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl	S
45	H	$-CF_3$	$-CF_3$	(4-acetyl)piperazin-1-yl	S
46	H	$-CF_3$	$-CF_3$	$-NH-CH_2-(2-C_6H_4Cl)$	S
47	H	$-CF_3$	$-CF_3$	$-N(Et)-(CH_2)_2-OH$	S
48	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-CH_3$	S
49	H	$-CF_3$	$-CF_3$	$-NH-C(CH_3)_2-CH_2-OH$	S
50	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(cyclohexyl)	S
51	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(4-pyridyl)	S
52	H	$-CF_3$	$-CF_3$	$-N(Et)-CH_2$-(4-pyridyl)	S
53	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-NH$-(2-pyridyl)	S
54	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(2-pyridyl)	S
55	H	$-CF_3$	$-CF_3$	[4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl	S
56	H	$-CF_3$	$-CF_3$	4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl	S
57	H	$-CF_3$	$-CF_3$	4-(2-furoyl)piperazin-1-yl	S
58	H	$-CF_3$	$-CF_3$	$-NH-CH$(cyclopropyl)$(4-C_6H_4-OCH_3)$	S
59	H	$-CF_3$	$-CF_3$	$-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$	S
60	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_2-OH)$-Ph	S
61	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_3)-CH(OH)$-Ph	S
62	H	$-CF_3$	$-CF_3$	-NH-(1-benzylpiperidin-4-yl)	S
63	H	$-CF_3$	$-CF_3$	1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl	S
64	H	$-CF_3$	$-CF_3$	$-N(CH_3)-(CH_2)_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)	S
65	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(3-pyridyl)	S
66	H	-Cl	-Cl	$-NH-(CH_2)_2-CH(CH_3)_2$	S
67	H	-Cl	-Cl	$-NH-CH(CH_3)_2$	S
68	H	-Cl	-Cl	$-NH-CH_2-CH(CH_3)_2$	S
69	H	-Cl	-Cl	$-NH-CH_2-C(CH_3)_3$	S

70	H	-Cl	-Cl	-NH-CH_2-CF_3	S
71	H	-Cl	-Cl	-NH-CH_2-CCH	S
72	H	-Cl	-Cl	-N[$(CH_2)_2CH_3$]$_2$	S
73	H	-Cl	-Cl	-NH-$(CH_2)_2$-(4-C_6H_4Cl)	S
74	H	-Cl	-Cl	(4-methyl)piperidin-1-yl	S
75	H	-Cl	-Cl	-N[CH_2-$CH(CH_3)_2$]$_2$	S
76	H	-Cl	-Cl	pyrrolidin-1-yl	S
77	H	-Cl	-Cl	-NH-$(CH_2)_3$-(imidazol-1-yl)	S
78	H	-Cl	-Cl	1,2,3,4-tetrahydroisoquinolin-2-yl	S
79	H	-Cl	-Cl	(2,6-dimethyl)morpholin-4-yl	S
80	H	-Cl	-Cl	4-[(3-trifluoromethyl)phenyl]piperazin-1-yl	S
81	H	-Cl	-Cl	azepin-1-yl	S
82	H	-Cl	-Cl	(4-benzoyl)piperidin-1-yl	S
83	H	-Cl	-Cl	-NH-$(CH_2)_3$-Ph	S
84	H	-Cl	-Cl	-NH-(4-hydroxycyclohexyl)	S
85	H	-Cl	-Cl	-NH-(3-hydroxycyclohexyl)	S
86	H	-Cl	-Cl	4-hydroxypiperidin-1-yl	S
87	H	-Cl	-Cl	3-hydroxypiperidin-1-yl	S
88	H	-Cl	-Cl	3-hydroxypyrrolidin-1-yl	S
89	H	-Cl	-Cl	-NH-$(CH_2)_2$-OH	S
90	H	-Cl	-Cl	-NH-$(CH_2)_3$-OH	S
91	H	-Cl	-Cl	-NH-$(CH_2)_4$-OH	S
92	H	-Cl	-Cl	-NH-$(CH_2)_6$-OH	S
93	H	-Cl	-Cl	-NH-$(CH_2)_2$-(morpholin-4-yl)	S
94	H	-Cl	-Cl	-NH-CH_2-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl	S
95	H	-Cl	-Cl	(4-acetyl)piperazin-1-yl	S
96	H	-Cl	-Cl	-NH-CH_2-(2-C_6H_4Cl)	S
97	H	-Cl	-Cl	-N(Et)-$(CH_2)_2$-OH	S
98	H	-Cl	-Cl	-NH-$(CH_2)_3$-CH_3	S
99	H	-Cl	-Cl	-NH-$C(CH_3)_2$-CH_2-OH	S
100	H	-Cl	-Cl	-NH-CH_2-(cyclohexyl)	S
101	H	-Cl	-Cl	-NH-$(CH_2)_2$-(4-pyridyl)	S
102	H	-Cl	-Cl	-N(Et)-CH_2-(4-pyridyl)	S
103	H	-Cl	-Cl	-NH-$(CH_2)_3$-NH-(2-pyridyl)	S
104	H	-Cl	-Cl	-NH-$(CH_2)_2$-(2-pyridyl)	S
105	H	-Cl	-Cl	[4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl	S
106	H	-Cl	-Cl	4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl	S

107	H	-Cl	-Cl	4-(2-furoyl)piperazin-1-yl	S
108	H	-Cl	-Cl	-NH-CH(cyclopropyl)(4-C_6H_4-OCH_3)	S
109	H	-Cl	-Cl	-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)	S
110	H	-Cl	-Cl	-NH-CH(CH_2-OH)-Ph	S
111	H	-Cl	-Cl	-NH-CH(CH_3)-CH(OH)-Ph	S
112	H	-Cl	-Cl	-NH-(1-benzylpiperidin-4-yl)	S
113	H	-Cl	-Cl	1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl	S
114	H	-Cl	-Cl	-N(CH_3)-(CH_2)$_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)	S
115	H	-Cl	-Cl	-NH-CH_2-(3-pyridyl)	S
116	H	-CF_3	-CF_3	-NH-(CH_2)$_2$-CH(CH_3)$_2$	O
117	H	-CF_3	-CF_3	-NH-CH(CH_3)$_2$	O
118	H	-CF_3	-CF_3	-NH-CH_2-CH(CH_3)$_2$	O
119	H	-CF_3	-CF_3	-NH-CH_2-C(CH_3)$_3$	O
120	H	-CF_3	-CF_3	-NH-CH_2-CF_3	O
121	H	-CF_3	-CF_3	-NH-CH_2-CCH	O
122	H	-CF_3	-CF_3	-N[(CH_2)$_2$$CH_3$]$_2$	O
123	H	-CF_3	-CF_3	-NH-(CH_2)$_2$-(4-C_6H_4Cl)	O
124	H	-CF_3	-CF_3	(4-methyl)piperidin-1-yl	O
125	H	-CF_3	-CF_3	-N[CH_2-CH(CH_3)$_2$]$_2$	O
126	H	-CF_3	-CF_3	pyrrolidin-1-yl	O
127	H	-CF_3	-CF_3	-NH-(CH_2)$_3$-(imidazol-1-yl)	O
128	H	-CF_3	-CF_3	1,2,3,4-tetrahydroisoquinolin-2-yl	O
129	H	-CF_3	-CF_3	(2,6-dimethyl)morpholin-4-yl	O
130	H	-CF_3	-CF_3	4-[(3-trifluoromethyl)phenyl]piperazin-1-yl	O
131	H	-CF_3	-CF_3	azepin-1-yl	O
132	H	-CF_3	-CF_3	(4-benzoyl)piperidin-1-yl	O
133	H	-CF_3	-CF_3	-NH-(CH_2)$_3$-Ph	O
134	H	-CF_3	-CF_3	-NH-(4-hydroxycyclohexyl)	O
135	H	-CF_3	-CF_3	-NH-(3-hydroxycyclohexyl)	O
136	H	-CF_3	-CF_3	4-hydroxypiperidin-1-yl	O
137	H	-CF_3	-CF_3	3-hydroxypiperidin-1-yl	O
138	H	-CF_3	-CF_3	3-hydroxypyrrolidin-1-yl	O
139	H	-CF_3	-CF_3	-NH-(CH_2)$_2$-OH	O
140	H	-CF_3	-CF_3	-NH-(CH_2)$_3$-OH	O
141	H	-CF_3	-CF_3	-NH-(CH_2)$_4$-OH	O
142	H	-CF_3	-CF_3	-NH-(CH_2)$_8$-OH	O

143	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(morpholin-4-yl)	O
144	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl	O
145	H	$-CF_3$	$-CF_3$	(4-acetyl)piperazin-1-yl	O
146	H	$-CF_3$	$-CF_3$	$-NH-CH_2-(2-C_6H_4Cl)$	O
147	H	$-CF_3$	$-CF_3$	$-N(Et)-(CH_2)_2-OH$	O
148	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-CH_3$	O
149	H	$-CF_3$	$-CF_3$	$-NH-C(CH_3)_2-CH_2-OH$	O
150	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(cyclohexyl)	O
151	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(4-pyridyl)	O
152	H	$-CF_3$	$-CF_3$	$-N(Et)-CH_2$-(4-pyridyl)	O
153	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_3-NH$-(2-pyridyl)	O
154	H	$-CF_3$	$-CF_3$	$-NH-(CH_2)_2$-(2-pyridyl)	O
155	H	$-CF_3$	$-CF_3$	[4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl	O
156	H	$-CF_3$	$-CF_3$	4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl	O
157	H	$-CF_3$	$-CF_3$	4-(2-furoyl)piperazin-1-yl	O
158	H	$-CF_3$	$-CF_3$	$-NH-CH$(cyclopropyl)$(4-C_6H_4-OCH_3)$	O
159	H	$-CF_3$	$-CF_3$	$-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$	O
160	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_2-OH)$-Ph	O
161	H	$-CF_3$	$-CF_3$	$-NH-CH(CH_3)-CH(OH)$-Ph	O
162	H	$-CF_3$	$-CF_3$	-NH-(1-benzylpiperidin-4-yl)	O
163	H	$-CF_3$	$-CF_3$	1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl	O
164	H	$-CF_3$	$-CF_3$	$-N(CH_3)-(CH_2)_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)	O
165	H	$-CF_3$	$-CF_3$	$-NH-CH_2$-(3-pyridyl)	O
166	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-CH(CH_3)_2$	S
167	-Cl	H	$-CF_3$	$-NH-CH(CH_3)_2$	S
168	-Cl	H	$-CF_3$	$-NH-CH_2-CH(CH_3)_2$	S
169	-Cl	H	$-CF_3$	$-NH-CH_2-C(CH_3)_3$	S
170	-Cl	H	$-CF_3$	$-NH-CH_2-CF_3$	S
171	-Cl	H	$-CF_3$	$-NH-CH_2-CCH$	S
172	-Cl	H	$-CF_3$	$-N[(CH_2)_2CH_3]_2$	S
173	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-(4-C_6H_4Cl)$	S
174	-Cl	H	$-CF_3$	(4-methyl)piperidin-1-yl	S
175	-Cl	H	$-CF_3$	$-N[CH_2-CH(CH_3)_2]_2$	S
176	-Cl	H	$-CF_3$	pyrrolidin-1-yl	S
177	-Cl	H	$-CF_3$	$-NH-(CH_2)_3$-(imidazol-1-yl)	S
178	-Cl	H	$-CF_3$	1,2,3,4-tetrahydroisoquinolin-2-yl	S

179	-Cl	H	$-CF_3$	(2,6-dimethyl)morpholin-4-yl	S
180	-Cl	H	$-CF_3$	4-[(3-trifluoromethyl)phenyl]piperazin-1-yl	S
181	-Cl	H	$-CF_3$	azepin-1-yl	S
182	-Cl	H	$-CF_3$	(4-benzoyl)piperidin-1-yl	S
183	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-Ph$	S
184	-Cl	H	$-CF_3$	-NH-(4-hydroxycyclohexyl)	S
185	-Cl	H	$-CF_3$	-NH-(3-hydroxycyclohexyl)	S
186	-Cl	H	$-CF_3$	4-hydroxypiperidin-1-yl	S
187	-Cl	H	$-CF_3$	3-hydroxypiperidin-1-yl	S
188	-Cl	H	$-CF_3$	3-hydroxypyrrolidin-1-yl	S
189	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-OH$	S
190	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-OH$	S
191	-Cl	H	$-CF_3$	$-NH-(CH_2)_4-OH$	S
192	-Cl	H	$-CF_3$	$-NH-(CH_2)_6-OH$	S
193	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-$(morpholin-4-yl)	S
194	-Cl	H	$-CF_3$	$-NH-CH_2-$(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl	S
195	-Cl	H	$-CF_3$	(4-acetyl)piperazin-1-yl	S
196	-Cl	H	$-CF_3$	$-NH-CH_2-(2-C_6H_4Cl)$	S
197	-Cl	H	$-CF_3$	$-N(Et)-(CH_2)_2-OH$	S
198	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-CH_3$	S
199	-Cl	H	$-CF_3$	$-NH-C(CH_3)_2-CH_2-OH$	S
200	-Cl	H	$-CF_3$	$-NH-CH_2-$(cyclohexyl)	S
201	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-$(4-pyridyl)	S
202	-Cl	H	$-CF_3$	$-N(Et)-CH_2-$(4-pyridyl)	S
203	-Cl	H	$-CF_3$	$-NH-(CH_2)_3-NH-$(2-pyridyl)	S
204	-Cl	H	$-CF_3$	$-NH-(CH_2)_2-$(2-pyridyl)	S
205	-Cl	H	$-CF_3$	[4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl	S
206	-Cl	H	$-CF_3$	4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl	S
207	-Cl	H	$-CF_3$	4-(2-furoyl)piperazin-1-yl	S
208	-Cl	H	$-CF_3$	$-NH-CH($cyclopropyl$)(4-C_6H_4-OCH_3)$	S
209	-Cl	H	$-CF_3$	$-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$	S
210	-Cl	H	$-CF_3$	$-NH-CH(CH_2-OH)-Ph$	S
211	-Cl	H	$-CF_3$	$-NH-CH(CH_3)-CH(OH)-Ph$	S
212	-Cl	H	$-CF_3$	-NH-(1-benzylpiperidin-4-yl)	S
213	-Cl	H	$-CF_3$	1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl	S
214	-Cl	H	$-CF_3$	$-N(CH_3)-(CH_2)_3-$(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)	S

215	-Cl	H	$-CF_3$	$-NH-CH_2-(3\text{-pyridyl})$	S
216	H	$-CF_3$	$-CF_3$	$-NH-CH_2-(2,4-C_6H_3Cl_2)$	O

and pharmaceutically acceptable salts thereof.

16. Compounds according to any one of the preceding claims which are active as potassium channel openers.

17. A pharmaceutical composition comprising a compound according to claim 1 or 2 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

18. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as diabetes comprising a compound according to claim 1 or 2 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

19. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as diabetes comprising a compound according to any of the claims 1 - 15 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

20. The pharmaceutical composition according to claim 17 to 19 in the form of an oral dosage unit or parenteral dosage unit.

21. A pharmaceutical composition according to claim 17 to 19 wherein said compound is administered as a dose in a range from about 0.05 mg to 1000 mg, preferably from about 0.1 mg to 500 mg and especially in the range from 50 mg to 200 mg per day.

22. A compound according to any one of the claims 1 - 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use.

23. A compound according to any one of the claims 1 - 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or prevention of diseases of the endocrinological system, such as diabetes.

24. The use of a compound according to any one of the claims 1 - 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form as a medicament.

25. The use of a compound according to any of the claims 1 - 15 for preparing a medicament.

26. The use of a compound according to any one of the claims 1 - 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of diseases of the endocrinological system, such as diabetes.

27. A method of treating or preventing diseases of the endocrinological system, such as diabetes in a subject in need thereof comprising administering an effective amount of a compound according to any of the claims 1 - 15 to said subject.

28. A process for the manufacture of a medicament to be used in the treatment or prevention of diseases of the endocrinological system, such as diabetes which process comprising bringing a compound of formula I according to any of the claims 1 - 15 or a pharmaceutically acceptable salt thereof into a galenic dosage form.

29. Any novel feature or combination of features as described herein.